REMARKS

The present Amendment and the following Remarks are submitted in response to the Office Communication mailed September 12, 2007. Applicant thanks the Examiner for rejoining the species of criteria for selecting features of the predictive marker set and for rejoining the species multiple myeloma with the myelomas group. Applicant also thanks the Examiner for reviewing the information disclosure statement.

Claims 1 and 2 are being amended. New claim 43 is being added. Support for an amendment to claim 1 can be found in the specification at, for example, paragraph [0015]. Some of the amendments to claim 1 may be judged in light of MPEP § 2181 (Rev. 6, Sept. 2007). Support for new claim 43 can be found in the specification at, for example, paragraph [0098]. Claim 30 is withdrawn. Claims 1, 2, 4, 5, 7, 10, 29, 31-33, 42 and 43 are pending upon entry of these amendments.

No new matter is being added. The Objection and Rejections raised by the Examiner in the Communication are addressed below.

Specification

The Examiner objected to some typographical errors in the specification. Replacement paragraphs correcting those errors are provided herein. As Applicant has found additional typographical errors, the paragraphs which contain those errors also are corrected herein. One correction replaces browser-executable code with information identifying the reference named in the code. Withdrawal of these objections is respectfully requested.

Another correction, to paragraph [0050], is to correct an obvious typographical error. In this paragraph, the error (labeling positive response predictive markers as "non-predictive markers, (NR)") is an obvious error in light of a later sentence in the same paragraph (wherein negative response predictive markers are given the same name). The correction of this error is obvious to one skilled in the art in light of later paragraphs, *e.g.*, paragraph [0082] which refers to both types of markers in the same sentence "responsive or non-predictive markers." Applicant respectfully submits that this correction is not adding new matter and requests that it be incorporated.

Paragraph 7. Rejections of the Claims Under 35 U.S.C. §112, Second Paragraph

Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 were rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Several rejections fell under this section. Each rejection is treated separately in the following paragraphs.

Paragraph 8. Claim 1 and its dependent claims 2, 4, 5, 7, 10, 29, 31-33 and 42 were considered indefinite for reciting the allegedly relative term "significant." The Examiner felt that the term "significant expression level" is not defined by the claim and that the specification does not provide a standard for ascertaining the requisite degree of expression difference. As a result, one of skill in the art allegedly would not be reasonably apprised of the scope of the invention. Applicant respectfully traverses this rejection.

Applicant respectfully brings the Examiner's attention to paragraph [0041] at pages 11-12 of the specification. In this paragraph, "significant" expression is defined with regard to the standard error of the assay employed to assess expression. This paragraph discusses the possibility that some features may be overexpressed (expressed at a higher level than normal) and that some features may be underexpressed (expressed at a lower level than normal). This disclosure is supplemented by an overview in paragraph [0016] (page 6), which discusses controls and standards against which to judge over- and under-expression. Assay methods are provided and Applicant provides further guidance in generating results for comparing expression levels, *e.g.*, paragraphs [0081], [0083], [0084], [00102], and [00103] provide options of deriving normalized or relative expression levels for nucleotide or antibody detection. Applicant submits that one of skill in the art of expression profiling would be familiar with statistical methods relating to the particular assay being used and would be able to recognize a level of expression that is less than or greater than the standard error of the measurement. In view of the content of the specification and the level of skill in the art,Applicant respectfully requests that this rejection be withdrawn.

Paragraph 9. Claim 1 and its dependent claims 2, 4, 5, 7, 10, 29, 31-33 and 42 were considered indefinite because all of the predictive markers in tables 1 and 4 are drawn allegedly to accession numbers and no sequence listing data is found. Accession numbers are not considered unique identifiers required for identification of mRNAs, because they can be changed and the cited sequence may vary over time. The Examiner requested that Tables 1 and 4 be amended to refer to sequences listed in a sequence listing. Applicant respectfully traverses this rejection.

A rejection under 35 U.S.C. §112, second paragraph must consider whether the claims are precise and unambiguous to a reasonable degree of particularity and distinctness. The claims need to be judged on the content of the disclosure, the teachings of the prior art and the interpretation by one with ordinary skill in the art (MPEP §2173.05). A claim to a chemical compound is not indefinite merely because a structure is not presented (MPEP §2173.05(t)) and may be claimed by a name that adequately describes the material to one skilled in the art. The Examiner is respectfully invited to review paragraph [0032] which defines a "marker' as "at least one of the nucleic acids or proteins associated with Affymetrix probe set identifiers" listed in the table. The Affymetrix Probe set ID numbers are provided for each of the markers in Table 1; Table 4 refers to the marker numbers identified in Table 1.

The NCBI accession numbers and descriptions are provided for reasons which include 1) for convenience to aid in conceptualization of genes which typically are identified by the probe sets; and 2) to provide the practitioner with additional sequences to devise reagents for measuring expression levels. The probe sets are a defined set of sequences compiled on each array by the manufacturer and the sequences are available to the public. Product literature provided by the manufacturer (see, *e.g.*, the Affymetrix website technical support section) lists the sequences included in each probe set. These sequences are established under each probe set identifier by the manufacturer upon devising the array and do not change. Each probe set is composed of multiple sequences and it would be an undue burden to list all of these publicly-available sequences for every marker in the tables. For example, the sequence file provided by Affymetrix technical support for the U133A array lists eleven probe sequences for marker 149 (Probe set ID 221569_at), each about 23-26 nucleotides in length. To provide this number of sequences for every marker listed in Tables 1-3 would mean creating a sequence listing of thousands of sequences which are exact copies of what already is available to the public. Even NCBI retains and makes available dated revisions of sequences (see the "Check sequence revision history" link on the NCBI website; see Exhibits A and B for the history of marker 149 and the sequence version from March 20, 2002) so, if desired, one can retrieve a sequence in the form in which it was available as of the priority date of the present application. As described in the specification, to practice the claimed invention, one of skill in the art can use the probe sets themselves, the nucleotide sequence or polypeptide sequence in the NCBI record or any combination or portion thereof to select and devise reagents by methods known in the art and supplemented in the specification at for example at paragraphs [0087]-[00110]. One of skill in the art would recognize the probe set identifier and NCBI designation as definite guides within the means for selecting the reagents and methods to measure the expression levels.

By reference to the tables which precisely identify probe set identifiers for each marker and the common designations available at the time of filing, the claims particularly point out and distinctly claim the subject matter. The information in the tables is the precise information needed to practice the claimed methods. The specification directs the skilled practitioner to the public Affymetrix information to see more about the probe set and the common designation, additional information on which, including nucleic acid and protein sequences, is publicly available at the NCBI. Thus, the tables provide the skilled practitioner with multiple avenues to choose to practice the claimed invention, either use the nucleic acid probes as published by Affymetrix, use nucleic acid probes derived from the NCBI gene entry or use polypeptide probes derived from the NCBI protein entry. Therefore, the sequences are not the essential components, but the guidance to direct the skilled practitioner publicly available sequences useful to select detection tools is the essential component. That guidance is amply provided by the claimed reference to the tables and the disclosure in the specification. In view of these remarks, Applicant respectfully requests withdrawal of the rejection

Paragraph 10. Claim 1 and its dependent claims 2, 4, 5, 7, 10, 29, 31-33 and 42 were considered indefinite because allegedly "it is unclear which, if any predictive marker set, including Table 4, will indicate that a patient is responsive or non-responsive to bortezomib therapy." Applicant respectfully traverses this rejection.

Applicant notes that while the rejection is based on Table 4, this is a species that illustrates a marker set which could result from the method of claim 1, and not necessarily the subject of claim 1. The method of claim 1 invites the practitioner to use the markers of Table 1 to devise a predictive marker set. This response will explain both how to determine whether a patient is responsive or non-responsive by following the method using Table 1 and how to determine responsiveness of a patient using Table 4.

Using Table 1. The practitioner would select markers from Table 1 and determine expression levels for those markers in tumor samples and compare the levels to control levels. The specification, *e.g.*, beginning at paragraph [0081] through paragraph [0086] provides insight on building such information for making the comparisons or applying statistical methods (provided in the Examples or known to those skilled in the art) which allow judgment of responsiveness and non-responsiveness. For statistical analysis of expression results, the ranking system of Table 1 provides information which can guide selection of markers and statistical method which applies preferably to each marker (see paragraphs [00221]-[00229]) and whether the expression level indicates responder or non-responder.

Using Table 4. Table 4 is compilation of markers which resulted when a practitioner applied a weighted voting statistical method to the expression results of markers in Table 1 for a sample obtained from a new patient. Paragraph [00236] provides an explanation of how to interpret expression results using Table 4. The "Weight" column in Table 4 is the signal-to-noise ratio in the equation (see the text in the parentheses in this paragraph). The "Decision boundary" column in Table 4 provides the value which is subtracted from the log expression of the marker so the result can be multiplied by the weight. As explained in paragraph [00236], when one obtains a sum of the results of these calculations for all the markers in the table, one judges whether the patient's tumor is sensitive or resistant (see paragraphs [00220] and [00221]).

In summary, the specification provides the skilled practitioner markers, methods for measuring expression levels of the markers and analyzing the results. Table 1 provides guidance in selecting markers and statistical methods (if desired) and insight in applying the results to obtain a decision on responsiveness or non-responsiveness. Table 4 is the result where the Applicant performed this work in a weighted voting statistical method. In view of these remarks, the claims are not indefinite and this rejection should be withdrawn.

Paragraph 11. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 were considered indefinite for allegedly omitting steps. In the interest of furthering prosecution, a step was added to claim 1(the remaining claims

dependent thereon) to recite isolating a patient sample. In view of this amendment, withdrawal of this rejection is respectfully requested.

Paragraph 12. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 were considered indefinite for allegedly omitting essential elements, amounting to a gap between the elements. The Examiner is of the opinion that a specific control is needed to compare the expression level of the features to determine whether the expression level is significant. In response, claim 1 is being amended to clarify the steps and antecedence within the claim. In view of this amendment, withdrawal of the rejection is respectfully requested.

Rejection of the Claims Under 35 U.S.C. §112, First Paragraph

Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 were rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention. This rejection is divided into three sections, which will be treated separately.

Paragraph 13. The claims were rejected for allegedly identifying the markers in Tables 1 and 4 only by accession numbers and not providing sequence information. The Examiner observed that sequences corresponding with accession numbers may vary over time. This variance was determined to result in undue experimentation for one of skill in the art to identify and use the sequences in the table for the method as claimed. The Examiner alleges that there is insufficient guidance for one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. Applicant respectfully traverses this rejection.

As discussed above, the markers in the tables are identified by the probe set identifier which refers to a set of oligonucleotide probes which do not change. What the set of oligonucleotide probes binds to is inherent in the composition of that probe set. The marker is identified by that probe set number and by providing NCBI accession numbers, the tables provide guidance to additional sequences associated with that marker. It is well within the skill in the art to retrieve the sequences from the public sources (Affymetrix and NCBI, even for the version available as of the priority date of the present application) and devise reagents to measure the expression levels by well known methods known to the art and supplemented by description, e.g., at paragraphs [0087]-[00110]. While there is work involved in practicing the claimed method, the work does not require undue experimentation for one of skill in the art to practice the claimed method with a reasonable expectation of success. Withdrawal of this rejection is respectfully requested.

Paragraph 14. The claims were rejected because allegedly no nexus has been established between determining the level of expression of the features in the predictive marker set of Table 4 and determining a bortezomib regimen for treating myeloma because those of ordinary skill in the art allegedly recognize that identification of prognostic markers is unpredictable. To support that allegation, the Examiner cited a

publication by Mulligan et al. in which additional work was discussed. Applicant respectfully traverses this rejection. This statement was made in the context of noting that the studies described in the publication (and in the present patent application) used samples from patients who had relapsing and refractory multiple myeloma. The comment noted that another set of samples from newly diagnosed patients might be worth studying for confirming the results where previous treatment could not possibly be contributing to the results. Another aspect of this comment is that in the studies, the patients were treated with single agents, while frequently, they are treated with a combination of agents. So samples from such patients would be desired to confirm the results of the present studies. Applicant notes that since this study, the work determining markers to aid in therapy and diagnosis has continued. Submitted herewith in a supplemental IDS is a publication (Agnelli et al. 2005) wherein the authors used probe sets from the Affymetrix arrays to study the expression of three markers in samples from newly diagnosed patients. One of these markers, CCND2, marker no. 841 in the present application, was confirmed to play a role in one of the multiple myeloma tumor subtypes.

The Examiner introduced the Tockman et al. publication to illustrate the allegedly large amount of research needed to validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence and confirm marker predictive value in prospective population trials. The Examiner alleged that little is known in the prior art about the nature of the invention in this allegedly unpredictable art and that the specification provided insufficient guidance for enabling one to practice the invention. This notion respectfully is traversed.

Applicant notes that the Tockman et al. article was published in 1992, ten years before the priority date of the present application and well before many of the advances in biochemistry and molecular biology from which the present studies benefit. For example, the human genome was sequenced during the intervening time and many advanced detection and quantification methods were developed and many additional reagents became available. One note regarding the Agnelli et al. reference is that it evidences the public availability of gene expression data for multiple myeloma (see page 7297 and reference 16 cited therein (Zhan et al, March, 2002). So the skilled practitioner by the priority date of this application even had data with which to compare expression results obtained when practicing the claimed invention. Second, the Tockman et al. article is focused on methods for early detection and diagnosis of tumor using samples from sputum which may not necessarily comprise tumor cells. The present claims focus on confirmed tumor samples. Third, it is understandable that Tockman et al article would state that a prospective clinical study would be needed to confirm their results because of their focus on detection of lung cancer in asymptomatic individuals. However the studies in the present application are performed on clinical specimens. The prospective clinical specimens are inherent to the working examples disclosed in the present specification. The focus of the present application is not whether the individuals have cancer, but whether the markers can predict whether a treatment is suitable

for the patients. The outcome of the clinical trial was taken into account when the markers were classified as responsive or non-predictive.

In summary, the state of the art and the working examples provided in the present application enable the skilled practitioner to practice the claimed invention without undue experimentation. In view of these remarks, withdrawal of the rejection is respectfully requested.

Paragraph 15. The claims were rejected because allegedly, no nexus has been established between any expression level of the markers in Table 4 and any indication that a patient is responsive or non-responsive to bortezomib therapy. Allegedly, the specification has not taught the use of the marker set of table 4 for determining a bortezomib therapy regimen for any patient. Allegedly, there is no teaching as to what levels of expression of the markers in Table 4 will be significant for indicating responsiveness or nonresponsiveness. The Examiner concluded from these alleged shortcomings that undue experimentation would be required for one of skill in the art to make and use the invention as claimed. This rejection is respectfully traversed.

The response for Paragraph 10. on previous page 11 explained how to use Table 4 to determine whether a new multiple myeloma patient will be sensitive or resistant to bortezomib therapy. Briefly, paragraph [00236] teaches that the vote weights obtained after using the weight and decision boundary and the expression level of each Table 4 marker in the sample are added to obtain a sum which determines responsiveness or nonresponsiveness of the patient's tumor. An example of applying the weighted voting method was used in the example providing Table 5 (paragraph [00249]). In that example, the patient was predicted to be non-responsive when the five vote weights were added. Applicant submits that the usage of this method is enabling from the teachings in the specification and the content of Table 4. The only thing the skilled practitioner would have to do besides the vote weight calculations is determine the expression level of the markers in Table 4. The methods for determining expression, e.g., mRNA detection, are well known in the art and are supplemented in the application, e.g., at paragraphs [0087]-[00101] and further supplemented by the working example beginning at paragraph [00199]. In view of these remarks, withdrawal of this rejection is respectfully requested.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1, 2, 4, 5, 7, 10, 29, 31-32 and 42 were rejected under 35 U.S.C. §112, first paragraph on the grounds that the specification does not contain an adequate written description of the claimed invention. This rejection is divided into three parts which are treated separately in the following paragraphs.

Paragraph 16. The claims were rejected for lack of written description because of the statements of further work (discussed above in regard to Mulligan et al and Tockman et al), the number of markers and statistical possibilities in Table 1, the lack of sequences in the application, the Examiner's lack of confidence that Tables 4, 5, or 6 would work as described or that these tables would be a representative

number of species in the genus to allege that there is not a written description of the claimed genus. This rejection is respectfully traversed.

Applicant notes that the specification also provides Tables 2, 3, 7 and 8, which describe additional species of markers. Tables 2 and 3 provide species which are associated with time to progression or progressive disease and Tables 7 and 8 are disclose markers associated with biological annotations or tumor cell lines. As discussed above, the identification of the markers in the tables is sufficient for one of skill in the art to recognize the structures associated with the claimed methods. By the working examples represent markers identified in a clinical setting and Table 1 identifies markers as being associated with responsiveness or non-responsiveness. At the time of filing, one of skill in the art would recognize the genus of methods claimed in claim 1, using the markers in Table 1, of which Tables 1, 4, 5, 6, 7, and 8 are included as method species is adequately described. As discussed above, the specification does provide the structures recognizable and retrievable to one of skill in the art and methods are described to utilize the structures. In view of these remarks, withdrawal of the rejection is respectfully requested.

Paragraph 17. The claims were rejected for allegedly broadening the scope of the description in the application as filed. This rejection is respectfully traversed. Applicant submits that perhaps [0050] is a typographical error and that paragraph [0049] is more helpful to understand support for the claim. Paragraphs [0010]-[0012], [0014], [0017], [0063]-[0065], [0075], [0078] can be added to the list, as claim 1 has been amended. Withdrawal of this rejection is respectfully requested.

Paragraph 18. Claim 42 was rejected for allegedly having no clear support in the specification. This rejection is respectfully being traversed by pointing to paragraph [0017]. In view of this remark, withdrawal of this rejection is respectfully requested.

Rejoinder

Applicant submits that claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 and new claim 43 will be found allowable, and the application is allowable with respect to the group elected after the Restriction Requirement mailed January 8, 2007. Applicant believes that now, the Examiner, under MPEP § 821.04, as noted in the Restriction Requirement, can undertake the review of the withdrawn claim 30 and nonelected species, which depend from or otherwise include all the limitations of the allowable product claims. In the next Office communication, Applicant respectfully requests comment on these withdrawn claims after rejoinder.

CONCLUSION

The foregoing amendments and remarks are being made to place the Application, having both elected and rejoined claims, in condition for allowance. Applicant respectfully requests the timely

allowance of the pending claims because, in view of these amendments and remarks, Applicant respectfully submits that the objection to the specification and the rejections of the claims under 35 U.S.C. § 112 are overcome. Applicant believes that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned. If the Examiner disapproves of Applicant's amendments and remarks in this response, Applicant requests a prompt mailing of a notice to that effect.

This paper is being filed timely as a request for a three month extension of time is filed concurrently herewith. No additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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